

## The changing life science patent landscape

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**What have we learned from 20 tumultuous years of patent law in the life sciences? Is patenting likely to be as important for the industry in the future?**

Over the past two decades, patent law in the life sciences has been buffeted by numerous controversies. With courts, legislatures and patent offices all responding, one could be forgiven for believing that the main constant has been change. In the following article, we look back at some of the major events in life science intellectual property (IP) law and business practice over the past 20 years and then suggest where IP practice in the life sciences may be heading in the coming years.

### Controversy and change

In the United States, the standards that govern which inventions can be patented have shifted dramatically over the past 20 years. In the 1990s, these standards were quite liberal, and patent lawyers routinely filed broad claims on what might have been considered unpatentable basic research. But as patents proliferated, they raised the specter of onerous and costly licensing negotiations for downstream innovators<sup>1</sup>. Such ‘anti-commons’ concerns led the US Patent and Trademark Office (USPTO) to ultimately narrow, or even reject, the broadest or most speculative claims on early-stage research<sup>2</sup>.

More recently, two additional areas have generated controversy: patents on diagnostic testing and so-called secondary patents on the small-molecule chemical therapies approved by the US Food and Drug Administration (FDA). As to the former, critics have claimed that costs outweigh benefits: that such patents pose undue impediments to patient, physician and scientist autonomy as well as patient access<sup>3</sup>. On the lat-



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ter, critics have charged that biopharmaceutical firms are using patents to develop not new chemical compositions but trivial improvements to already approved drugs. On this view, ‘secondary patents’ serve to perpetually ‘evergreen’ market exclusivity for certain drugs<sup>4</sup>. Indeed, objections to secondary patents were a major point of contention during the recent negotiations over the Trans-Pacific Partnership Agreement<sup>5</sup>. Such objections also formed the basis for the Indian Supreme Court’s rejection of Novartis’s (Basel, Switzerland) patent on a derivative of Gleevec (imatinib mesylate), a leukemia and gastrointestinal stromal tumor therapy<sup>6</sup>.

Life science patent controversies have also caught the attention of the US Supreme Court. The vast literature decrying persistent problems of vagueness and overbreadth in software and business method patents<sup>7</sup> appears to have influenced the Supreme Court’s decision making. The Court’s unanimous 2012 decision

in *Mayo Collaborative Services v. Prometheus Laboratories*<sup>8</sup> rejected patent claims on adjusting the dosage of a thiopurine drug based on measuring the drug’s metabolite levels. In rejecting those claims, the Supreme Court relied on cases involving software, among other technologies, to reach a sweeping holding that patent claims encompassing “laws of nature” are illegitimate unless they contain an additional “inventive step.” Similarly, the Supreme Court’s unanimous 2013 decision in *Association of Molecular Pathology v. Myriad Genetics*<sup>9</sup> famously rejected all patent claims directed to isolated genomic DNA. There, the Court cited trans-technological concerns about patenting information, holding that patent claims encompassing “products of nature” were invalid unless “markedly different” from their natural counterparts.

These Supreme Court decisions stressed policy concerns that broad patents on foundational research may unduly impede follow-on

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innovation. Unfortunately, however, the decisions are widely viewed as having failed to explicitly integrate these policy concerns into workable legal tests. Because the claims at issue in the *Mayo* case were quite narrow, for example, the case likely undermines many existing diagnostic patents—both broad and narrow. The challenge to diagnostic patents has been exacerbated by a recent decision of the US Court of Appeals for the Federal Circuit, *Ariosa Diagnostics v. Sequenom*<sup>10</sup>. In that decision, the court read *Mayo* as requiring it to invalidate patent claims covering a pioneering, noninvasive, prenatal genetic testing technology. Several judges have since voiced their concern about the impact of *Mayo* and other decisions on life sciences R&D.

### Evolving business practices

In other instances, evolving business practices have caused decision makers to rethink the limits of patents. In its 2013 decision in *Federal Trade Commission v. Actavis*<sup>11</sup>, for example, the US Supreme Court struck down agreements in which pioneer biopharmaceutical firms settle generic patent challenges by paying substantial sums to the challenger. These agreements, the Court concluded, were anticompetitive under antitrust law, despite the patent protections surrounding the challenged drugs. Importantly, most of the prohibited settlements have involved secondary patents<sup>4</sup>.

The US Congress has also responded to evolving business practices. In recognition of the international nature of patent protection, the procedural changes implemented by the 2011 Leahy-Smith America Invents Act (AIA) have largely harmonized US law on patent priority with other jurisdictions<sup>12</sup>. In a partial recognition of the increased costs of patent litigation, the AIA also created a robust administrative apparatus for challenging patent validity, the Patent Trial and Appeals Board (PTAB). The most controversial patent validity challenges at the PTAB have involved the life sciences: challenges to patents on biopharma-

ceuticals brought not by generic manufacturers but by hedge funds that short the patent owner's stock<sup>13</sup>. Here, too, patent law and policy have not stood still. Numerous legislative bills have been proposed to address these, and other, unintended consequences of the ever-shifting patent landscape<sup>14</sup>.

### The centrality of nonpatent regulation

For both small molecules and diagnostics, a critical but often overlooked innovation policy lever has been nonpatent regulation. For small molecules, nonpatent regulation has worked synergistically with patents. A key reason patents, including secondary patents, have proved to be valuable is the strong linkage between patent law and FDA approval, a feature of the regulatory landscape since the 1984 Hatch-Waxman Act. As a consequence, any patent that a developer asserts is relevant to its approved product can be used to delay the regulatory approval of generics<sup>15</sup>. The relative importance of patents is further enhanced by the Hatch-Waxman Act's allowance for generic firms to rely on a developer's clinical trial data if the generics can demonstrate 'bioequivalence' to the original drug—studies that cost as little as a million dollars<sup>16</sup>. Perhaps unsurprisingly, then, empirical research indicates that the number of patents per drug for the cohort of drugs approved between 2000 and 2002 was roughly double that for the cohort of drugs approved around 1984, the year the Hatch-Waxman Act was passed<sup>4</sup>.

Conversely, a major reason patents have historically been less necessary for diagnostics than for therapeutics is the absence of mandatory FDA premarket approval. Although some diagnostic manufacturers of stand-alone kits have been required to seek FDA approval, laboratory-developed tests (LDTs) have been regulated only by the US Center for Medicare and Medicaid Services under the Clinical Laboratory Improvement Amendments (CLIA). CLIA's regulations assess only the test's analytical validity, not the accuracy with

which a test measures the presence or absence of a particular condition<sup>17</sup>. With the FDA now planning to apply its premarket review system for medical devices to at least some LDTs<sup>18</sup>, the capital investment—and number of patents—required to bring those tests to market is likely to increase substantially.

### The future

The pattern of constant change to the patent landscape may augur well for some life science technologies, but less so for others. Changes in patenting practice and law outside the United States have also affected technology, such as human embryonic stem cells (**Box 1**).

Going forward, the outlook for small-molecule therapeutics appears challenging. Although the USPTO has interpreted *Myriad* narrowly by allowing patent claims to naturally derived molecules so long as they possess different functions<sup>19</sup>, the extent to which courts will agree with the USPTO is unclear. Additionally, the Supreme Court's decision in *Actavis* limits the ability of small-molecule innovators to use secondary patents and reverse-payment settlements to evergreen their franchises.

Another potential threat, particularly for secondary patents, is the increasing frequency with which these patents are being challenged at the PTAB. Since the procedures were adopted in 2012, there have been almost 170 challenges to small-molecule drug patents through these avenues<sup>14</sup>. All of these changes are occurring against a background in which the R&D cost associated with bringing new drugs to market has increased<sup>20</sup>. The net consequence may be that small-molecule drugs with modest potential consumer markets may not be worth commercializing unless they are given extra regulatory protection. Many brand drug developers have already encountered difficulties in charging high-premium prices in markets outside of the United States (**Box 2**).

Although prospects for small-molecule drugs have diminished, those for biologics may have risen. Although R&D costs associated with bringing biologics to market have increased, and even though biologics patents may be vulnerable under *Myriad*, biologics are buffered from competition by several layers of protection independent of patents. Historically, a major buffer has been the absence of any generic pathway. And even though a 2010 law, the Biologics Price Competition and Innovation Act (BPCIA)<sup>21</sup>, provides a limited "biosimilar" pathway to rely on pioneer's clinical trial data, the BPCIA still appears quite burdensome for follow-on manufacturers. In addition, biologics are generally much more difficult to both manufacture and characterize

### Box 1 Beyond US borders

Because the US represents the largest market for life science products, rapid developments in US patent law are very important. At the same time, the law of other jurisdictions has also evolved considerably. In Europe, for example, much of this evolution has been driven by concerns about patents that are seen as contrary to public morality. The European Biotechnology Directive 98/44 prohibits patents seen as contrary to "public order" or morality, and specifically includes in this category patents on processes for cloning human beings, modifying the human germ line, and using human embryos for industrial or commercial purposes. In 2011, the European Court of Justice (CJEU) interpreted this directive to ban patents involving stem cells created through the destruction of human embryos<sup>25</sup>. But a 2014 CJEU decision partially narrowed the scope of the 2011 ban so as to exclude stem cells created through parthenogenesis<sup>26</sup>.

## Box 2 Compulsory licenses and drug pricing

In the United States, patent owners typically have no affirmative obligation to license their patents. Although the US government may use unlicensed patents if it compensates the patent owner<sup>27</sup>, it has rarely used this power for life science patents. And even when the federal government itself funds the patented research, and could therefore—in theory—“march in” and require patent holders to license their inventions, this has yet to occur in practice<sup>28</sup>. Internationally, however, the Trade-Related Aspects of Intellectual Property Rights Agreement allows its signatories to enact legislation permitting compulsory patent licenses in certain circumstances. Thailand, Brazil and India, among others, have issued compulsory license orders. Moreover, even the mere threat of compulsory licenses has encouraged pharmaceutical developers to lower their prices in response<sup>29</sup>. How different emerging economies will address the dual challenges of providing drug access to their populations and building life science innovation sectors remains to be seen.

analytically than small molecules. Developers guard manufacturing information very closely as a trade secret, and FDA guidance under the BPCIA not only requires biosimilar manufacturers to attempt to reverse engineer such processes—at great cost—but to conduct, at least partially, some of their own clinical trials. A follow-on approval process that costs hundreds of millions of dollars creates an obvious barrier to entry<sup>22</sup>. But even if FDA were to relax its regulatory standards, originator biologics manufacturers would still enjoy better market exclusivity than their small-molecule counterparts: a separate 12-year regulatory exclusivity period, 7 years longer than that provided to new chemical entities of small-molecule drugs.

Diagnostic testing firms, meanwhile, were once able to rely upon both patents and trade secrecy for protection. Although patents and trade secrecy over the same inventive territory arguably challenged the public policy goal of promoting disclosure, simultaneous reliance on both of these regimes was not uncommon<sup>23</sup>. With patents now in doubt, diagnostic firms may rely even more heavily on secrecy.

Secrecy in the area of diagnostics has engendered concern at the FDA. In the context of its general determination that it should now regulate LDTs, the FDA has emphasized the need for regulatory review of the nontransparent, “complex” algorithms on which many modern LDTs are based<sup>18</sup>. The FDA is not alone in its concern. The agency’s work in this area fol-

lows a prominent Institute of Medicine (IOM) report, issued in 2012, recommending the FDA ‘develop and finalize a risk-based guidance or regulation on bringing omics-based tests to FDA for review’<sup>24</sup>.

To be sure, FDA review—and regulatory exclusivities—can readily co-exist with trade secrecy. Indeed, at least for larger firms in the LDT space, trade secrecy combined with high regulatory barriers that hamper competition may represent a very attractive combination. But certain commentators have gone further, calling for greater transparency in data and analyses associated with biopharmaceutical innovation. They have emphasized the innovation-related benefits that could accrue from pooling many different types of biological data previously held in trade secret siloes and making these data more widely available to researchers<sup>23</sup>. How tensions between open science and trade secrecy will play out remains to be seen, and will likely depend heavily on trends in public funding of open data initiatives.

### Conclusions

Over the past 20 years, the patent structure surrounding life science innovation has changed substantially. If current trends continue, the future is likely to be one of diminishing returns to patents. In some cases, alternative incentive structures could be friendlier to larger firms than smaller firms.

Regardless, 20 years from now, when *Nature Biotechnology* celebrates 40 years of publication, others may be writing a similar article about trade secrets and regulatory exclusivities—rather than patents.

### COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

- Heller, M.A. & Eisenberg, R.S. *Science* **280**, 698–701 (1998).
- Rai, A. *Duke Law J.* **61**, 1237–1281 (2012).
- Cook-Deegan, R., Chandrasekharan, S. & Angrist, M. *Nature* **458**, 405–406 (2009).
- Hemphill, C.S. & Sampat, B. *Science* **339**, 1386–1387 (2013).
- Kapczynski, A. *N. Engl. J. Med.* **373**, 201–203 (2015).
- Novartis AG v. Union of India*, Civil Appeal No. 2706–2716 (Supreme Court of India, 2013).
- Bessen, J. & Meurer, M. *Patent Failure* (Princeton Univ., 2008).
- 132 S. Ct. 1289 (2012).
- 133 S. Ct. 2107 (2013).
- 788 F.3d 1371 (Fed. Cir. 2015).
- 133 S. Ct. 2223 (2013).
- Merges, R.P. *Berkeley Technol. Law J.* **27**, 1023–1046 (2012).
- Hemphill, T.P. *Regulation* **38**, 6–8 (2015).
- Rai, A.K. & Sherkow, J.S. *Letter to US Senate Committee on the Judiciary Concerning Inter Partes Review and Orange Book-Listed Patents* [http://papers.ssrn.com/sol3/papers.cfm?abstract\\_id=2623736](http://papers.ssrn.com/sol3/papers.cfm?abstract_id=2623736) (June 18, 2015).
- Eisenberg, R. & Crane, D. *Mich. Telecomm. Tech. Law Rev.* **21**, 197–262 (2015).
- Grabowski, H. et al. *FDA Law J.* **67**, 373–391 (2012).
- Sharfstein, J. *J. Am. Med. Assoc.* **313**, 667–668 (2015).
- FDA Fed. Regist.* **79**, 59776–59779 (2014).
- USPTO. *Fed. Regist.* **97**, 74618–74633 (2014).
- DiMasi, J.A., Grabowski, H.G. & Hansen, R.W. *Innovation in the pharmaceutical industry: new estimates of R&D costs* [http://csdd.tufts.edu/news/complete\\_story/cost\\_study\\_press\\_event\\_webcast](http://csdd.tufts.edu/news/complete_story/cost_study_press_event_webcast) (Tufts Center for the Study of Drug Development, Boston, November 18, 2014).
- Public Law No. 111–148, 124 Stat. 199 (2010).
- Price, W.N. II & Rai, A.K. *Science* **348**, 188–189 (2015).
- Cook-Deegan, R., Conley, J.M., Evans, J.P. & Vorhaus, D. *Eur. J. Hum. Genet.* **21**, 585–588 (2013).
- Micheel, C.M, Nass, S.J. & Omenn, G.S. (eds.) *Evolution of Translational Omics: Lessons Learned and the Path Forward* (Institute of Medicine, The National Academies Press, Washington, 2012).
- Brüstle v. Greenpeace eV*, Opinion of Advocate General. Case C-34/10 (CJEU Mar. 10, 2011).
- Int’l Stem Cell Corp. v. Comptroller Gen. of Patents*. Case C-364/13 (CJEU Dec. 18, 2014).
- 28 U.S.C. § 1498.
- Sherkow, J.S. *Wash. Law Rev.* **90**, 205–269 (2015).
- Reichman, J.H. *J. Law Med. Ethics* **37**, 247–263 (2009).